UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

March 18, 2009

MEMORANDUM

SUBJECT: Summary of Human Health Effects Data for the Inorganic Halides Registration Review Decision Document.

DP Barcode: 361013 **Case No.:** 4051
PC Codes: 013902, 013905, and 013907
CAS#: 1310-73-2

FROM: Nathan Mottl, Biologist N. Mottl 3-18-09
Team Two
Risk Assessment and Science Support Branch (RASSB)
Antimicrobials Division (7510P)

TO: K.Avivah Jakob, Chemical Review Manager
Regulatory Management Branch II
Antimicrobials Division (7510P)

Diane Isbell, Team Leader
Regulatory Management Branch II
Antimicrobials Division (7510P)

THRU: Norm Cook, Branch Chief Norm Cook 3/18/09
Risk Assessment and Science Support Branch (RASSB)
Antimicrobials Division (7510P)

Nader Elkassabany, Team Leader N Cook for 3/18/09
Team Two
Risk Assessment and Science Support Branch (RASSB)
Antimicrobials Division (7510P)

Introduction

The Antimicrobial Division (AD) Registration Review Team has evaluated the status of the human health assessments for inorganic halides case (RED case 4051). The inorganic halides case includes three active ingredients magnesium chloride (PC Code 013902) and sodium bromide (PC Code 013907) and sodium chloride (PC Code 013905). The case used to include calcium chloride (PC Code 075605). However, this active ingredient was canceled. Sodium bromide is used as a microbiocide to control algae, bacteria and fungi in pasteurizer and cannery, cooling water recirculation systems, pulp and paper mill systems and ornamental ponds and aquaria. In addition, sodium bromide also includes uses in swimming pools, spas, fruit and vegetable wash, egg wash and sugar beet wash. Sodium chloride is a disinfectant, sanitizer, algaecide, bactericide and fungicide when mixed with other active ingredients (e.g., sodium dichloroisocyanurate dehydrate) is used to treat feeding and watering appliances and re-circulating and non-recirculating irrigation systems, equipment and hard non porous surface premises in greenhouses, nurseries, shade houses, etc. It is mixed in low concentrations (1.5% a.i.) with other active ingredients (e.g., potassium peroxymonosulfate) as a disinfectant, fungicide and algaecide. Magnesium chloride is conventional pesticide and used only as an herbicide (not an antimicrobial chemical) on ice plant which is both a decorative and invasive plant which is commonly located in chaparral habitats such as California, Australia and the Mediterranean.

The team looked at the hazard and exposure databases for the inorganic halides, which included the antimicrobial uses of magnesium chloride, sodium bromide and sodium chloride, and attempted to determine whether changes in science policy or deficiencies in the databases materially affected the overall risk picture. It should be noted that the Agency is also concerned that under certain circumstances sodium bromide can oxidize to the carcinogen bromate in swimming pools and in drinking water and the Agency will be assessing the overall aggregate risk based on the potential formation of bromate.

According to the 1993 RED Facts document, sodium bromide was first registered as a pesticide in the U.S. in 1975. Currently 80 pesticide products contain the active ingredient sodium bromide. An exemption from the requirement of a tolerance is specified in 40 CFR 180.940c for sodium bromide when used in food contact sanitizing solutions. The exemption from the requirement of tolerance limits bromide states... *When used for ready to use food contact sanitizing solutions, the end-use concentration of all bromide-producing chemicals in the solution is not to exceed 200 ppm total available halogen.* Sodium bromide contains egg washes, fruit and vegetable wash uses and a sugar beet wash use. Typically AD would establish an exemption for these particular uses.

Sodium chloride was first registered in 1954. At present, 3 pesticide products contain sodium chloride as an active ingredient. Only 1 pesticide product contains magnesium chloride, which was first registered in 1993.

The primary source of information for this assessment is the most recent 2005 Bromine TRED which included risk assessments of uses of potassium bromide and sodium bromide as food contact sanitizers (USEPA 2005a); residential and dietary (excludes food contact sanitizers) uses of sodium bromide (USEPA 2005b); and the Inorganic Halides RED (1993). Toxicity endpoints were selected in the 2005 Bromine TRED. No new toxicity data for the inorganic halides have been submitted to the Agency, since the Agency completed the Inorganic Halides RED. A comprehensive listing of the documents considered is presented in this document. The purpose of this screen is to determine whether sufficient data are available to support registration review, whether new human health assessments are needed to support registration review, and to report why the Agency feels it may appropriate to conduct new risk assessments under the registration review process.

Magnesium chloride is a white solid with a melting point of 116-118 °C and is extremely soluble in water(1 gm/0.6 ml) has low volatility, and dissociates completely to magnesium and chloride ions when added to water. Sodium chloride a.k.a. table salt is a clear, crystalline solid with a melting point of 801°C. It is extremely soluble in water (35.7 g/100 mL at 20 °C), and has a neutral pH. It dissociates completely to sodium and chloride ions when it is added to water. Sodium chloride has a very low vapor pressure (<1E-6 torr). Sodium bromide is a white, crystalline solid with a melting point of 747 °C and is similar to sodium chloride. It is also extremely soluble in water (47.6g/100 mL at 20 °C), and has a neutral pH. It dissociates completely to sodium and bromide ions when it is added to water. Sodium bromide has a low volatility.

Although this registration review focuses on sodium bromide, it is also incumbent upon the Agency to assure that the aggregate of all nonoccupational exposures to bromide residues of toxicological concern results in a reasonable certainty of no harm to human populations as mandated by FQPA. There are a number of additional antimicrobials that also release bromide and, hence, act against microbes via the oxidizing activity of hypobromous acid (HBrO) just as sodium bromide does. Upon release of bromide from these other brominating antimicrobials, additional oxidative steps occur and equilibria are established between all of the acid and ion species of bromide described above for elemental sodium bromide. Each of the Reregistration Eligibility Decision Cases or Registration Review Cases listed below is currently on a different schedule. The chemical cases thus far known or expected to require aggregation with any sodium bromide residues of concern are:

- Bromine chloride (Br2). Registration Review Case 4015. P.C. Code 008701. CAS No. 7726-95-6. 2009 Docket. D360976
- Bromine. Reregistration Case No.: 4015. CAS No.: 7726-95-6. 2009 Docket.
- Ammonium bromide (NH4Br). Registration Review Case 5008. P.C. Code 000352. CAS No. 12124-97-9. 2012 Docket. D360680
- 3-Bromo-1-chloro-5,5-dimethyl-2,4-imidazolidinedione (a hydantoin). Registration Review Case 5005. P.C. Code 006322. CAS No. 126-06-7. 2009 Docket.
- 1-Bromo-3-chloro-5,5-dimethyl-2,4-imidazolidinedione (a hydantoin). Registration Review Case 3055. P.C. Code 006315. CAS No. 16079-88-2. RED issued 9/30/04.

- 1,3-Dibromo-5,5-dimethyl-2,4-imidazolidinedione (a hydantoin). Registration Review Case 3055. P.C. Code 006317. CAS No. 77-48-5. RED issued 9/30/04.
- 1-Bromo-3-chloro-5-ethyl-5-methyl-2,4-imidazolidinedione (a hydantoin). Registration Review Case 5101. P.C. Code 128989. CAS No. 91112-66-2. 2015 Docket (first registered 3/5/04).

Exposures to bromate ion and concomitant risks associated with the registered uses of chemicals in each case provided above will be assessed individually during the risk assessment stage of the Registration Review for each case. Upon completion of the risk assessment stages of all antimicrobials generating bromate ion, the exposures to bromate ion derived from each of these antimicrobial cases will be aggregated with any other known sources, if co-exposure is determined to be likely.

Section 1. Chemical Identities

Table 1. Chemical Identity	
Common Name	Sodium Bromide
CAS name	Sodium Bromide
PC Code	013907
CAS registry number	7647-15-6
Registration Review Case No.	4051
Empirical Formula	NaBr

Table 2. Chemical Identity	
Common Name	Salt or Common Salt
CAS name	Sodium Chloride
PC Code	013905
CAS registry number	7646-14-5
Registration Review Case No.	4051
Empirical Formula	NaCl

Table 3. Chemical Identity	
Common Name	Magnesium Chloride
CAS name	Magnesium Chloride
PC Code	013902
CAS registry number	7786-30-3
Registration Review Case No.	4051
Empirical Formula	MgCl

Section 2. Toxicology

The Agency has reviewed all toxicity studies submitted for inorganic halides (e.g., sodium chloride and sodium bromide) and has determined that the toxicological database is sufficient. The toxicological database for the inorganic halides (sodium bromide and sodium chloride) case is currently comprised of published and unpublished studies either submitted to the Agency or obtained directly from published open literature.

Magnesium chloride can be extracted from brine or sea water and is abundant in nature. The FDA considers magnesium chloride as generally recognized as safe (GRAS) for foods under 21 CFR 184.1426. According to the jacket of the only existing label magnesium chloride has an acute toxicity category IV for acute oral, inhalation, dermal and eye irritation, and dermal sensitization. Magnesium chloride would dissociate in water completely to magnesium and chloride ions, which are essential constituents of the body and present in many foods

Sodium chloride, commonly known as salt, sea salt and table salt is abundant in nature and is commonly used to season or preserve food. It is hypothesized that consumption of salt in excess of the minimum daily requirement may contribute to high blood pressure in some individuals. The FDA considers sodium chloride as generally recognized as safe (GRAS) for use in foods under 21 CFR 182.70. Data from the existing RED indicates that sodium chloride has an acute toxicity category III for acute oral (rat) and eye irritation. It is only a mild skin irritant (acute toxicity category IV). The acute dermal, inhalation and skin sensitization studies were waived for the technical active ingredient. However, product specific toxicity studies have been submitted.

The Agency does not require repeated dose toxicity tests with sodium chloride because it dissociates in water completely to sodium and chloride ions, is an essential constituent of the body and present in many foods. For man, the daily requirement of sodium chloride is about 1 g (17 mg per kg) indicating that salt is of low toxicity. Based on limited exposure, the amount incidentally ingested or through dermal contact is expected to negligible compared to the amount of salt already present in most foods and is already present in the body.

Elemental bromine occurs in the diatomic state as Br_2 and is a natural element normally found as bromide in living organisms and the environment. In aqueous state in the presence of sunlight, oxidizing agents or alkaline conditions bromate is formed from bromide. With respect to bromide and potassium/sodium bromide there is no toxicological differences. However, bromate is considered more hazardous from a toxicological perspective. Sodium salts of bromide have been used for many years in prescription and proprietary sedatives. Consequently, the health effects of bromides following oral exposure are well known. The central nervous system depressant effects of the bromide salts in humans occur when administration is repeated daily at dose levels of 1 to 2 grams per day. Exposures from antimicrobial use are expected to be significantly less. Data from the existing Bromine TRED indicates that in technical form sodium bromide is acute toxicity category III for acute oral (rat) and dermal (rabbit). It is a mild skin irritant (toxicity category IV) and eye irritant (toxicity category IV). It is not a skin sensitizer. The acute inhalation studies were waived in the exiting RED.

The Agency did not require additional repeated dose toxicity data in the 1993 inorganic halides RED or the more recent 2005 Bromine TRED. The Report of the Antimicrobial Division Toxicology Endpoint Selection Committee reported that no toxicological endpoints were selected based on low dermal and inhalation exposures based on existing labeling requirements and low concentrations in swimming pool water. In addition, low dietary exposure because labeling requirements recommend a potable water rinse on fruits and vegetables and sanitizers are used in low concentration. Inhalation exposure to bromide is not anticipated because of its low volatility.

No toxicological endpoint was established for the Bromine TRED. Risk assessments were conducted for sodium bromide based on the residential and dietary uses and the Agency did not report any risks in either of the risk assessments (U.S. EPA 2005a and U.S. EPA 2005b) and occupational exposure appear to be minimal. The Agency does not expect toxicological endpoints will be established for sodium bromide.

Toxicity Database for Bromide

Subchronic Oral Toxicity

Maternal effects were observed for rats at the LOAEL of 300 mg/kg/day (MRID 55794601) in a rat developmental study. The primary effects consisted of decreased body weight gain. A NOAEL of 100 mg/kg/day was established. The rats were administered 99.84% sodium bromide was administered by gavage from gestation days six to fifteen at dose levels of 0, 100, 300, and 1000 mg/kg/day. Fetal effects were seen at significant maternal toxicity of 1,000 mg/kg/day. Other effects seen at the 1,000 mg/kg/day dose level included unsteady gait, weakness, and loss of coordination, reduced body tone and hair loss.

In a subchronic oral toxicity study (MRID 41833601), ethanolammonium perbromide was administered by daily gavage to Charles River rats at dose levels of 0, 2, 20, and 200 mg/kg/day for four weeks. Signs of toxicity were limited to the 200 mg/kg/day dose level. Salvation was reported along with 'noisy respiration.' Other signs of toxicity included decrease in food intake during the last week. Hematological parameters such platelet, RBC count and hemoglobin were significantly elevated.

Clinical chemistry increases such as aspartate amino-transferase, creatinine, albumin, total protein and cholesterol were also increased. Additionally urinary volume was increased and proteinuria increases were also noticed. Finally, histopathological hyperkaratosis and acenanosis of the stomach were also noticed.

Other Studies Submitted from the Scientific Literature for Sodium Bromide

In addition to the submitted studies, there was additional data presented in the scientific literature. The most significant toxicity studies were available in the scientific literature. This data was not converted into mg/kg/day, however. In 1989, the Food and Agricultural Organization of the United Nations and the World Health Organization (FAO/WHO) summarized available animal toxicity studies.

In rats fed NaBr in food, high dose levels of NaBr in food (19200 ppm) caused rats to show motor incoordination in their hind legs and poor grooming behavior. Concentration of NaBr was high enough to displace 50% of the chloride in the plasma, brain, kidneys and liver. In recent developmental study in rats indicate that pre- and postnatal exposure to high levels (250 mg % NaBr affects postnatal growth and brain development

Cancer from Bromate

The Agency is concerned that under certain circumstances sodium bromide can oxidize to bromate, which is a carcinogenic to laboratory test animal. The Agency will rely on the recent IRIS database for bromate toxicological endpoints to develop cancer assessments. This is the approach used in the most recent risk assessment (D321793). According to IRIS (IRIS, 2009) there was clear evidence that that bromate had the potential to induce carcinogenicity.

> *Three key studies (Kurokawa et al., 1986a, 1986b; DeAngelo et al., 1998) demonstrate the carcinogenicity of bromate in rats. All studies were well conducted, with an appropriate route of exposure and adequate numbers of animals. Several aspects of these bioassay studies support the conclusion that bromate has the potential to be a human carcinogen. First, tumors were observed at multiple sites, including the kidney (adenomas and carcinomas), the thyroid (follicular cell adenomas and carcinomas), and the peritoneum (mesotheliomas). In DeAngelo et al. (1998) the mesotheliomas arose from the* tunica vaginalis testis *and spread throughout the peritoneal cavity on the serosal surfaces of many organs. Kurokawa et al. (1986a, 1986b) do not specify the origin of the peritoneal mesotheliomas observed. Whereas male rats had tumors at all three sites, only kidney tumors were observed in female rats. However, the kidney tumors in female rats developed in the absence of the significant toxicity observed in the male rats.*
>
> *Second, a clear dose-response relationship existed in tumor incidence and in severity/progression of tumors. Kurokawa (1986a) observed a progression in severity from renal dysplastic foci, a preneoplastic lesion, through renal adenomas to renal carcinoma as the dose increased. Kurokawa et al. (1986b) observed dose-response relationships for kidney tumors in both male and female*

rats. Kurokawa (1986a) observed dose-response relationships for two other tumor types, mesotheliomas and thyroid follicular cell, in male rats. DeAngelo et al. (1998) observed dose-response relationships for all three tumor types in rats.

According to the latest IRIS database information, 'under the current *Guidelines for Carcinogen Risk Assessment* (USEPA, 1986), bromate would be classified as B2, probable human carcinogen. Under the *Proposed Guidelines for Carcinogen Risk Assessment* (USEPA, 1996), bromate should be evaluated as a likely human carcinogen by the oral route of exposure. Insufficient data are available to evaluate the human carcinogenic potential of bromate by the inhalation route." The link to the IRIS database is provided below.

http://www.epa.gov/ncea/iris/subst/1002.htm

EPA will be relying on the robust database of published toxicological studies when selecting a carcinogenic slope factor.

Section 3. Dietary Assessment

Dietary

Dietary (food and drinking water) exposures of concern are not anticipated for magnesium chloride and sodium chloride based on low exposures and low toxicity of salt from antimicrobial products using labeled products with low concentrations of magnesium chloride and sodium chloride. The Food and Drug Administration (FDA) considers sodium chloride as generally recognized as safe (GRAS) for use in foods under 21 CFR 182.170.

Sodium chloride, an essential constituent of the body and present in many foods, exhibits acute and chronic toxic effects when ingested in excessive amounts. Excess sodium chloride may induce hypertension in rats. There is a strong genetic component in the hypertensive response, and by selective breeding, strains of "spontaneusly" hypertensive rats have been developed. Hypertension has been evoked by excess sodium chloride in the food or drinking water of dogs but the effects were reversible and related to osmotic factors. Salt appetite is an important expression of personal preference in relation to diet, and salt contributes to palatability of foods. For some, salt-containing foods have important cultural values. Foods in which salt is important for preparation or preservation are a prominent component of many diets. The causes of hypertension in man are related to genetic and environmental factors: race, family history, variations in endocrine and kidney function, degree of obesity, and life-style. Although the findings of epidemiological studies suggest a relationship between salt intake and onset of hypertension, the evidence that salt consumption is a major factor in causing hypertension is not conclusive. For man, the daily requirement of sodium chloride is less than 1 g (17 mg per kg), an amount exceeded by that present as a naturally-occurring ingredient of most diets.

The Food and Drug Administration (FDA) also considers magnesium chloride as generally recognized as safe (GRAS) for use in foods under 21 CFR 184.1426.

Magnesium is a dietary essential. It is involved in myriad metabolic reactions and is necessary for the activity of many intracellular enzymes. Also, with certain other cations, it is important in electrolyte balance. Magnesium is present in fruits, vegetables, grains, milk, meat and fish and the natural content of these foods is the major source of the current dietary intake. The Food and Nutrition Board, NRC, has recommended that cereal grain products be fortified with magnesium in view of potential risk of deficiency among significant segments of the population. The usual adult intake is about 300mg or less per day from all sources and the contribution of food additives to total magnesium intake is very small. The administration of magnesium sulfate in very high doses to humans occasionally has resulted in severe and even fatal episodes, especially in the presence of pre-existing disease. These occurrences should not be prejudicial to the use of magnesium salts as foods ingredients since the dosages given were orders of magnitude greater than the daily intake of magnesium added to food. While chronic toxicity data are lacking, the status of magnesium as a ubiquitous and essential dietary ingredient for the maintenance of homeostatic and bioenergetic mechanisms leads to the opinion that none of the available evidence suggests any probable hazard when any of the GRAS compounds of magnesium is used as a food ingredient. In view of the foregoing, The Select Committee concludes that: There is no evidence in the available information on magnesium carbonate, magnesium chloride, magnesium sulfate, magnesium hydroxide, magnesium oxide, magnesium stearate, dibasic magnesium phosphate and tribasic magnesium phosphate that demonstrates, or suggests reasonable grounds to suspect, a hazard to the public when they are used at levels that are now current and in the manner now practiced, or which might reasonably be expected in the future.

An exemption from the requirement of a tolerance is specified in 40 CFR 180.940c for sodium bromide when used in food contact sanitizing solutions. The exemption from the requirement of tolerance limits bromide states... *When used for ready to use food contact sanitizing solutions, the end-use concentration of all bromide-producing chemicals in the solution is not to exceed 200 ppm total available halogen.* In addition, sodium bromide contains a fruit and vegetable wash uses and a sugar beet wash use. In 2005, EPA developed a risk assessment to reassess the sodium bromide risks as a food contact sanitizer. In this assessment, EPA concluded that "the use of sodium bromide is unlikely to pose a significant hazard to the general public or any population subgroup (USEPA 2005a)."

Additionally in 2005, EPA developed another assessment EPA reassessed the dietary risks of fruit and vegetable wash and sugar beets and did not report risk exceedances. Additional labels (EPA Reg # 1706-179) indicate that sodium bromide is used in egg wash water systems. It should be noted that there were no toxicological endpoints established in the Bromine TRED, risks were not expected and a quantitative dietary assessment was not developed and will likely not be needed for this registration review.

Drinking Water

Sodium bromide (NaBr) in the presence of water, rapidly forms both sodium hydroxide (NaOH), hydrobromic acid (HBr) and hypobromous acid (HBrO). The HBr

dissociates to form H+ and Br- and the HBrO dissociates to form H+ and hypobromite ion (BrO-). The BrO- may be oxidized by a stronger oxidizing agent such as ozone (O_3) or hypochlorite ion (ClO-) to form bromic acid (HBrO3) which dissociates to form H+ and bromate (BrO_3-). The rate of BrO_3- formation increases with increasing temperature and light intensity although the effect of pH on BrO_3- formation appears to depend on the specific combination of solution conditions. A number of experts in halogen chemistry claim that BrO_3- will rarely, if ever, form in nature. It is expected to form, however, during such anthropogenic activities as chlorination of outdoor pools, ozonation of drinking water, or use of a chlorobromohydantoin for sanitization. When in aqueous solution, all of the various forms of a halogen, such as those of Bromine noted above, will exist in an equilibrium or ratio that is dependent on a number of variables such as pH, temperature, concentrations, electrochemical environment, headspace, dissolved solutes, suspended materials, illumination, etc. Most of the chemical reactions involving the multiple Bromine species are disproportionation reactions, i.e., one Bromine compound simultaneously undergoes both oxidation and reduction such as the reaction of Br_2 with H_2O to yield Br-, BrO-, and 2H+.

Bromate

In aqueous state (e.g., swimming pools) in the presence of sunlight, oxidizing agents or alkaline conditions bromate is formed from bromide (see Hazel, W. 2009, D360680). There is a relationship between UV light and the oxidizer when forming bromate from sodium bromide applications. Bromate formation can also occur during ozonation. However, EPA has insufficient data to develop a trend on the conversion rate of sodium bromide to bromate ion based on the contributions of sodium bromide.

Certain registered outdoor sodium bromide use sites or those often directly discharged are likely to result in dietary exposure via drinking water. Such sites include pasteurizer and cannery water, cooling water recirculation systems water, and pulp and paper mill systems water. Although trace amounts of bromate ion could form under certain conditions, this highly oxidized form of sodium bromide is not expected to survive in the environment long enough for water from these commercial/industrial discharges and limited outdoor uses to reach a potable water source. Ultimately, virtually all sodium bromide chloride residues in the environment (including raw water) will exist as Na+ and Br- as a result of the dissociation of NaBr and HCl and by oxidation of organic matter (including microbes) by the oxidized sodium bromide species. The Br- in water contributed by use of sodium bromide is not expected to be distinguishable from the background, naturally-occurring levels. Therefore, there is no need to quantify any exposure to bromate ion that may result from introduction of sodium bromide residues into the environment. It is the oxidation of this naturally-occurring bromide ion during drinking water ozonation that is likely to contribute virtually the entire bromate ion to which humans are exposed.

The EPA's Office of Water has established a Maximum Contaminant Level (MCL) for residual bromate in drinking water at 10 µg/L (10 ppb or 0.01 ppm). This MCL represents all sources of residual bromate ion in drinking water whether they are naturally-occurring/background sources or anthropogenic (including pesticidal).

Section 4. Occupational/Residential Exposure

An occupational and/or residential exposure assessment is required for an active ingredient if (1) certain toxicological criteria are triggered and (2) there is potential exposure to handlers (mixers, loaders, applicators, etc.) during use or to persons entering treated sites after application is complete. For magnesium chloride, sodium chloride and sodium bromide, the toxicological criteria are not triggered. Therefore, occupational and residential risk assessments are not required for magnesium chloride, sodium bromide and sodium chloride.

Magnesium Chloride

For magnesium chloride the most common use would be spraying ice plant. The label (84396-30) indicates that the application would be performed by a pressure sprayer to residential lawns, ornamental gardens, interior plantscapes, and golf courses. Based on the low toxicity, of this product handler and post-application assessments would not be required.

Sodium Chloride

For sodium chloride the most predominant use would be wiping, moping and spraying applications which would be restricted to occupational use and dermal post-application exposure to wet surfaces. These exposures are expected to be minimal.

Sodium Bromide

For sodium bromide there are currently 78 registered labels. Most of the uses include handler exposure to mixing/loading ready to use liquids, soluble concentrates, granulars, and tablets. Bromide biocides are primarily mixed in water for agricultural premises and equipment (egg wash systems, irrigation systems); industrial process water systems (cooling water, wastewater systems, pulp and paper, etc); residential pools and public access (pools, spas, hot tubs, etc.); and medical premises and equipment (instrument soak). Many of the larger water systems such as cooling towers and waste water systems would use closed systems for pumping liquids. However, the labels do not require specific engineering controls so open pouring would be expected. It appears that at least one label (EPA Reg # 70369-1) includes a use where a tablet is placed into a water spray bottle which used as a disinfectant for sinks, bathrooms, and floors.

For sodium bromide wiping, spraying, and mopping handler exposures would be expected with this use. In addition, residential handler exposures occur when users pour chemicals into pool water. Occupational and residential swimming exposure would be the largest predominant post-application activity. A risk assessment would only be needed for the bromate occupational and residential swimming exposures.

Bromate

The Agency is concerned that under certain circumstances sodium bromide can oxidize to bromate which is a carcinogen. In aqueous state (e.g., swimming pools) in the presence of sunlight, oxidizing agents or alkaline conditions bromate is formed from

bromide (see Hazel, W. 2009, DD). There is a relationship between UV light and the oxidizer when forming bromate from sodium bromide applications. However, EPA has insufficient data to develop a trend on the conversion rate of sodium bromide to bromate ion; therefore EPA will need additional exposure studies to develop a risk assessment. Justifications for the additional exposure studies are presented in Appendix A.

EPA received a 6(a)2 submission that indicated high concentrations of bromate in outdoor swimming pools when applying sodium bromide activated with $Ca(OCl)_2$ to produce hypobromous acid (Arch, 2005). EPA reviewed these data in the sodium bromide risk assessment (D321793). Although EPA developed a risk assessment for bromate ion concentrations based on the 6(a)2 submission, EPA has concernsregarding the pool water concentrations reported in the Arch (2005) study. In the previous review (D321793), EPA stated:

- *The concentration of bromate ion in swimming pools has not been adequately characterized. This assessment provides risk estimates at various bromate ion concentrations based on available data in the 6(a)2 submission and assumptions made based on the information available. Additional sampling would better characterize the risk estimates.*
- *Arch (2005) did not provide details on the sampling and analysis methods. No QA/QC data were included in the submission.*

In addition, the Agency received pool water concentration from the American Chemistry Council (ACC) on dihalodialkylhydantoin applications which generated low levels of bromate concentrations in outdoor swimming pools (ACC 2005). This study was also reviewed by EPA (D324327) and the conclusions included:

- *Neither data submission (ACC 2005 and Arch 2005) provided details of the sampling and analysis methods. No QA/QC data were included in either submission. ACC (2005) indicated that the pools were treated as per label directions but specifics were not provided. Finally, the ACC (2005) submission did not provide the individual data points for the bromate ion concentrations.*
- *The pool treatments in the Arch (2005) submission appear to be based on exaggerated applications of sodium bromide which may account for the higher bromate ion concentration in those pools.*

In conclusion, the Agency will consider any new data submitted on the concentrations of bromate in pool water as a result from the use of sodium bromide and would likely develop a new refined risk assessment for the swimming pool scenario in the future.

Section 5. Aggregate and Cumulative Exposure

In examining aggregate exposure, EPA takes into account the available and reliable information concerning exposures to pesticide residues in food and drinking water, and non-occupational pesticide exposures. Of the three inorganic halides (magnesium chloride, sodium chloride and sodium bromide), the only toxicological concern is from the breakdown product bromate ion which may form in the water after

sodium bromide is added to outdoor swimming pools. Magnesium chloride and sodium chloride do not produce bromate ion. Furthermore, there are no toxicological endpoints of concern for the inorganic halide compounds sodium bromide, sodium chloride or magnesium chloride. In fact the Food and Drug Administration (FDA) considers magnesium chloride and sodium chloride as GRAS for use in foods. In conclusion, EPA's database indicates limited evidence of any sub-chronic or chronic toxic effects through any route of exposure for magnesium chloride, sodium chloride, and sodium bromide. As a result, no aggregate assessment is needed for these compounds. EPA will only need an aggregate assessment for the sodium bromide breakdown product bromate ion.

EPA developed sodium bromide residential and aggregate assessments for sodium bromide in support of the Bromine TRED in 2005. Sodium bromide was assessed in the aggregate assessment for bromine because bromine breaks down into bromide (and under certain conditions it further breaks down into bromate ion). The Agency assessed the aggregate risks and believes there are no aggregate risks from sodium bromide itself based on limited evidence of any sub-chronic or chronic toxic effects through any route of exposure. However, bromate ion (a breakdown product of sodium bromide in outdoor swimming pool water) has been categorized as a probable human carcinogen and bromate cancer risks were identified as an Agency concern in the previous residential assessment which examined bromate exposure from swimming pool water. A quantitative aggregate cancer risk assessment was not conducted in 2005 for bromate ion. It should be noted that the previous residential assessment identified potential cancer risks. This assessment was based on limited data and, therefore additional data was requested on the formation of bromate ion in swimming pool water in order to accurately assess the residential risks. An updated residential assessment and a new aggregate risk assessment will be needed to assess possible exposures to bromate from all sources including the use of sodium bromide in swimming pools and drinking water exposures. These assessments will be conducted once acceptable swimming pool concentrations of bromate are submitted to the Agency.

At this time EPA has no evidence that magnesium chloride, sodium chloride and sodium bromide and breakdown products (bromate ion) have a common mechanism with other compounds, consequently a cumulative assessment will not be performed for either of these chemicals.

Section 6. Anticipated Data Needs

The Antimicrobial Division (AD) will not be requiring any further studies for sodium chlorate, sodium bromide or magnesium chloride. For sodium bromide, the Agency will be requiring the following studies for the swimming pool degradation product bromate (detailed justification is presented in Appendix A).

Occupational and Residential Applicator Exposure Data Needs

- (Special Study) Bromate Swimming Pool Water Concentrations
- (GLN 875.2700) Product Use Information
- (GLN 875.2900) Data Reporting and Calculations

o (GLN 875.3000) Non-dietary Ingestion Exposure

Section 7. Tolerances

An exemption from the requirement of a tolerance is specified in 40 CFR 180.940c for sodium bromide when used in food contact sanitizing solutions. The exemption from the requirement of tolerance limits bromide states... *When used for ready to use food contact sanitizing solutions, the end-use concentration of all bromide-producing chemicals in the solution is not to exceed 200 ppm total available halogen.*

Tolerances or an exemption from the requirement of tolerances may be needed for fruit and vegetable wash, sugar beet wash and egg wash.

Section 8. Overall Conclusions

The Agency reviewed the hazard and exposure databases for sodium chloride and sodium bromide and anticipates that no additional toxicity and exposure data will be needed for registration review. However, the EPA anticipates that additional occupational and residential handler assessments and aggregate assessments will be needed for bromate to ensure that the inorganic halides registration review case meets the safety standards established by FFDCA, as amended by FQPA.

Section 9. Reference

- ACC (2005). Swimmers Exposure to Bromates. Letter from Hasmukh Shah, ph.D. to Ms. Connie Welch, dated March 1, 2005.
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Appendix A: Exposure Guideline Study Justifications

Guideline	Study Title	Practical Utility of the Data
Special Study	Bromate Swimming Pool Water Concentrations	**1) What is the value of the study?** Under certain conditions (e.g., U.V. light, oxidation, temperature, etc.) sodium bromide can break down to bromate ion in swimming pool water. However, the existing study on bromate ion pool water concentrations has many limitations (see section 4) and has an insufficient amount of data to develop a trend on the conversion rate of sodium bromide to bromate ion due to a number of variables in outdoor swimming pools such as pH, temperature, application rates, reaction with UV light and pool water chemical oxidizers. Bromate concentrations in swimming pools are needed to assess incidental oral exposure from swimming in sodium bromide treated pool water. Initial risk assessments identified cancer risks (e.g. >1E-6) due to incidental ingestion of pool water. However, the study used for this assessment needed to be upgraded or a new study needs to be initiated based on exaggerated applications of sodium bromide, lack of QA/QC data, and limited details on the sampling methodology. **2) How will the data be used?** The available bromate ion concentrations in swimming pool water will be used to determine the magnitude of children's incidental ingestion exposure from bromate in swimming pool water. Bromate is a carcinogen and the bromate water concentrations in swimming pool water would be combined with non-dietary incidental ingestion exposure assumptions and cancer toxicity values to estimate carcinogenic risk from these exposures. **3) How could the data affect the risk assessment?** The data are needed to refine the cancer risk identified in the previous risk assessment or the data could be used to generate a new risk assessment. The data could either confirm that breakdown of sodium bromide to bromate in swimming pool water is significant under typical conditions, or the study may identify that bromate formation is minimal, or it could identify that only under certain unusual situations or misuses that bromate formation would occur. The assessment may confirm the findings of the existing risk assessments that bromate is a cancer concern (e.g. >1E-6), or after the Agency receives the data, the Agency may determine that cancer risk is not a concern (<1E-6) from this exposure scenario or after reviewing the study the Agency may determine that the magnitude of the cancer risk is different then the initial results.

		4) What is triggering the need for this data? The specific use triggering the criteria for the bromate concentration data is the potential for incidental oral exposure from the swimming pool use. Initial risk assessments identified cancer risks (e.g. >1E-6) due to incidental ingestion of pool water. However, EPA believed that the study submission that was used to understand pool water concentrations may have exaggerated applications of sodium bromide, which may account for the higher bromate ion concentration in those pools. In addition, limited details were available on the sampling and analysis methods and the QA/QC. The Agency would likely use this data to develop a risk assessment and make a safety finding and to determine whether labels need to be adjusted or refined.
875.2700 (Post Application)	Product Use Information	**1) What is the value of the study?** Product use information (label rates and pool chemical concentrations) for the post application data are needed so the risk assessor can gain better knowledge of how much sodium bromide is used in the swimming pool water. With this data, the assessor can understand the variability and uncertainties associated with different label applications of the product in pool water, use of pool chemicals, and a description of formation of bromate in swimming pool water. A description of what types of consumer products are treated, the influence of pool treatment chemicals, pH of water, etc. would provide for a comprehensive realistic assessment of potential post application exposures. **2) How would the data be used?** The listing of the end use consumer products would be used to define the exposure scenarios to be assessed in the risk assessment. For example, the product use must describe the scenario of use (bromide in swimming pool water and formation of bromate). **3) How could the data affect the risk assessment?** A complete description of consumer products treated would ensure that the risk assessment is inclusive of the types of exposures occurring during residential use. **4) What is triggering the need for this data?** The need for a risk assessment as needed under Registration Review would require that the risk assessor understands how the product is applied.
875.2900 (Post Application)	Data Reporting and Calculations	**1) What is the value of the study?** For all exposure studies this data requirement is required to facilitate the review of the data.

		2) How will the data be used? The study report and all raw data/calculations will be reviewed for the adequacy of the data. **3) How could the data affect the risk assessment?** The data are needed to interpret the residue data collected. **4) What is triggering the need for this data?** The data reporting requirement is triggered if a residue study or pool water concentration study is conducted.
875.3000 (Post Application)	Non-dietary Ingestion Exposure	**1) What is the value of the study?** The design of the non dietary ingestion exposure study can be combined with the bromate swimming pool water concentration study (875.2300) to determine the available bromate concentration in swimming pools **2) How will the data be used?** The available bromate concentration in pool water will be used to determine the magnitude of children's incidental exposure. **3) How could the data affect the risk assessment?** The data are needed to refine the risk estimates since risk concerns were found in the earlier 2005 sodium bromide risk assessment. **4) What is triggering the need for this data?** The criteria for the surface residue data are the potential for incidental oral exposure from swimming pool water.